Prognosis of Asymptomatic Patients With Hypertrophic Cardiomyopathy and Nonsustained Ventricular Tachycardia

Paolo Spirito, MD; Claudio Rapezzi, MD; Camillo Autore, MD; Paolo Bruzzi, MD, PhD; Pietro Bellone, MD; Paolo Ortolani, MD; Pietro V. Fraga, MD; Franco Chiarella, MD; Massimo Zoni-Berisso, MD; Angelo Branzi, MD; Dario Cannata, MD; Bruno Magnani, MD; Carlo Vecchio, MD

Background In the early 1980s, studies performed in highly selected referral patients with hypertrophic cardiomyopathy reported a strong association between the presence of brief episodes of ventricular tachycardia (VT) on ambulatory ECG monitoring and sudden death. These observations led to antiarrhythmic treatment in many patients with hypertrophic cardiomyopathy and brief episodes of VT. In recent years, however, a growing awareness of the potential arrhythmogenic effects of antiarrhythmic medications has raised doubts regarding such a therapeutic approach, particularly in less selected and lower-risk patient populations.

Methods and Results In the present study, we examined the prognostic significance of nonsustained VT in a population of 151 patients with hypertrophic cardiomyopathy who were asymptomatic or had only mild symptoms at the time of their initial ambulatory ECG recording. Of the 151 study patients, 42 had episodes of VT and 109 did not. The runs of VT ranged from 3 to 19 beats, with 35 patients (83%) having <10 beats. The number of runs of VT ranged from 1 to 12 in 24 hours, with 36 patients (86%) having ≤5 episodes of VT. Thus, in most patients, the episodes of VT were brief and infrequent. Follow-up averaged 4.8 years. Of the 151 study patients, 6 died suddenly, 3 in the group with VT and 3 in the group without VT. Two other patients, both in the group without VT, died of congestive heart failure. The total cardiac mortality rate was 1.4% per year in the patients with VT (95% CI, 0.4% to 3.5%) and 0.9% in those without VT (95% CI, 0.4% to 2.0%; P=.43). The relative risk of cardiac death for patients with VT was 1.4 compared with patients without VT (95% CI, 0.6 to 6.1). The sudden death rate was 1.4% per year in the patients with VT (95% CI, 0.4% to 3.5%) and 0.6% in those without VT (95% CI, 0.2% to 1.5%; P=.24). The relative risk of sudden death for patients with VT compared with those without VT was 2.4 (95% CI, 0.5 to 11.9). Of the 151 patients included in the study, 88 (58%) remained asymptomatic and were not treated with cardioactive medications during follow-up. Of these 88 patients, 20 were in the group with VT and 68 in the group without VT. None of these patients died.

Conclusions Our results show that cardiac mortality is low in patients with hypertrophic cardiomyopathy who are asymptomatic or only mildly symptomatic and have brief and infrequent episodes of VT on ambulatory ECG monitoring. Our findings also suggest that brief and infrequent episodes of VT should not be considered, per se, an indication for antiarrhythmic treatment in such patients. (Circulation. 1994;90:2743-2747.)

Key Words • hypertrophy • cardiomyopathy • death, sudden • tachycardia

Sudden and unexpected cardiac death is the most devastating feature of the natural history of hypertrophic cardiomyopathy and can be the first clinical manifestation of the disease in previously asymptomatic patients.1-3 Identification of those patients who are at increased risk of dying suddenly, however, remains a challenge. Two studies performed in the early 1980s independently reported an association between the presence of brief episodes of ventricular tachycardia (VT) and sudden death in patients with hypertrophic cardiomyopathy.4,5 On the basis of these observations, it was suggested that patients with nonsustained VT should be treated with antiarrhythmic medications.4,5 This led to antiarrhythmic treatment in many patients with hypertrophic cardiomyopathy and brief, asymptomatic episodes of VT.

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In recent years, however, a growing awareness of the potential arrhythmogenic effects of antiarrhythmic medications has raised doubts about this therapeutic approach.6 In addition, these two previous studies on the prognostic significance of VT were performed at major referral centers for hypertrophic cardiomyopathy; thus, these investigations were based on highly selected, high-risk patient populations and included patients with severe symptoms. Therefore, it is unclear whether these previous results can be applied to less selected patient populations that reflect more closely the characteristics of the overall population of patients with hypertrophic cardiomyopathy. This question is important in that brief episodes of VT are frequently identified during ambu-
latory ECG monitoring in many patients with hypertrophic cardiomyopathy who are asymptomatic.4-7,9

The present study was undertaken to assess the prognostic significance of nonsustained VT in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. The results of this investigation provide new elements on which to base the clinical management of these patients.

Methods

Patients

Between January 1983 and December 1991, 261 patients with hypertrophic cardiomyopathy were evaluated in the outpatient or inpatient services of the Divisione di Cardiologia, Ospedali Galliera, Genoa; the Istituto di Malattie dell'Apparato Cardiovascolare, Policlinico Sant'Orsola, Bologna; and the Cattedra di Clinica Medica, Ospedale Sant'Eugenio, Rome. Of these 261 patients, 155 fulfilled the following selection criteria and were included in the present study: (1) They had no symptoms of heart failure or only mild symptoms (New York Heart Association functional class I or II) at the time of their initial ambulatory ECG recording, (2) they had no history of recurrent syncope or recent syncope (within 6 months of the ambulatory ECG recording), and (3) they were not taking cardiovascular medications at the time of the ambulatory ECG recording.

Excluded Patients

To provide a complete picture of the clinical features and prognosis of the overall patient population from which our study patients were selected, clinical and follow-up data on the 106 excluded patients are reported in a separate section at the end of the "Results."

Final Study Population

Of the 155 patients initially included in the study, 4 were lost to follow-up. One of these 4 patients had VT and 3 did not have VT on their ambulatory ECG recording. The remaining 151 patients constitute the present study population. The 151 study patients ranged in age from 5 to 75 years (mean, 40±18 years); 106 (70%) were male. In each patient, the diagnosis of hypertrophic cardiomyopathy was based on the echocardiographic demonstration of a hypertrophied and nondilated left ventricle in the absence of other cardiac or systemic diseases that could produce comparable left ventricular hypertrophy.9,10 All the study patients were followed from the day on which their first ambulatory ECG recording was obtained through December 1991, or to the time of death if it occurred before December 1991. The period of follow-up ranged from 3 to 110 months (mean, 58 months).

Continuous 24- to 48-hour ECG recordings were obtained with a portable tape recorder and modified V1 and V6 leads. Ventricular tachycardia was defined as three or more premature ventricular depolarizations in succession. The presence of obstruction to left ventricular outflow under basal conditions was assessed from the echocardiogram on the basis of the magnitude and duration of systolic anterior motion of the mitral valve.12,13 Outflow obstruction was present in 41 patients and was absent in the remaining 110 patients.

Sudden and unexpected cardiac death was prospectively defined as witnessed, instantaneous collapse with subsequent death within minutes. Death was also classified as sudden if it occurred unexpectedly although unwitnessed, for example at night, in a patient without prior severe symptoms.

Statistical Methods

Data were expressed as mean±SD. The significance of the differences in continuous variables in the two study groups was assessed by the unpaired Student's t test; the significance of

<p>| Table 1. Baseline Characteristics of Patients With VT and Patients Without VT |
|--------------------|-----------------|-----------------|---|</p>
<table>
<thead>
<tr>
<th></th>
<th>Patients With VT (n=42)</th>
<th>Patients Without VT (n=109)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46±5</td>
<td>37±7</td>
<td>.005</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>31 (74)</td>
<td>74 (68)</td>
<td>NS</td>
</tr>
<tr>
<td>LVOT obstruction, n (%)</td>
<td>14 (33)</td>
<td>27 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>VT indicates ventricular tachycardia; LVOT, left ventricular outflow tract.</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

the differences in categorical variables was assessed by the χ2 test or Fisher's exact test, as appropriate. Rates of occurrence of death were computed as the ratio between the number of events in each group and the number of person-years of follow-up accumulated by the patients in the same group from the date of enrollment through December 31, 1991. In the assessment of the sudden cardiac death rates, the 4 patients who died from other causes were considered as censored at the time of death. CIs of rates were computed by use of the Poisson approximation, and the statistical significance of the differences in the rates in the study groups were assessed by the "exact" approach.14 Relative risk estimates were obtained by dividing death rates in the patients with and without VT. The 95% CIs were computed by use of the gaussian approximation of the logarithm of the relative risk.14 Kaplan-Meier curves showing the probability of survival were constructed for the occurrence of sudden cardiac death. A stratified analysis was used to adjust for the potentially confounding effect of age in the comparison of the occurrence of sudden death in patients with and without VT. In addition, a multivariate proportional-hazards model was fitted to the data to adjust simultaneously for both age and presence of outflow obstruction at initial examination.15

Results

Of the 151 patients included in the study, 42 had runs of VT on their initial ambulatory ECG recording and 109 did not. The runs of VT ranged from 3 to 19 beats, with 35 patients (83%) having <10 beats. The number of runs of VT ranged from 1 to 12 during a 24-hour recording, with 36 patients (86%) having ≤5 episodes of VT. The clinical profile of the patients with and without VT is summarized in Table 1. The patients with VT were significantly older than those without VT (46±15 years and 37±17 years, respectively; P=.005). Sex and prevalence of left ventricular outflow tract obstruction were not significantly different in the two groups.

During follow-up, 6 of the 151 study patients died suddenly and unexpectedly, 3 in the group with VT and 3 in the group without VT; each patient was in functional class I or II at the time of death. The three patients with VT who died suddenly had shown ≤5 episodes of VT during a 24-hour recording. Two other study patients, both in the group without VT, died of congestive heart failure. The clinical characteristics and medical therapy of these 8 patients are summarized in Table 2. During follow-up, two other patients died of noncardiac causes (one of cancer and one of homicide).

In the overall study population, the total mortality rate for cardiac causes (including both sudden death and death due to congestive heart failure) was 1.1% per year (95% CI, 0.5% to 1.9%). In the patients with VT, the total cardiac mortality rate was 1.4% per year (95% CI, 0.4% to 3.5%), and in the patients without VT, it
TABLE 2. Clinical Characteristics of Patients Who Died of Cardiac Causes During Follow-up

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age* / Sex</th>
<th>VT</th>
<th>LVOT Obstruction</th>
<th>History of Syncope</th>
<th>Cardiac Medications†</th>
<th>Functional Class III-VT</th>
<th>Modality of Death</th>
<th>Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17/M</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Amiodarone</td>
<td>-</td>
<td>Sudden</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>24/M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>β-Blocker</td>
<td>-</td>
<td>Sudden</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>35/M</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Quinidine</td>
<td>-</td>
<td>Sudden</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>36/M</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>β-Blocker</td>
<td>-</td>
<td>Sudden</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>69/F</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Flecainide</td>
<td>-</td>
<td>Sudden</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>75/M</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>β-Blocker</td>
<td>-</td>
<td>Sudden</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>31/M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>‡</td>
<td>+</td>
<td>Heart failure</td>
<td>39</td>
</tr>
<tr>
<td>8</td>
<td>37/F</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>‡</td>
<td>+</td>
<td>Heart failure</td>
<td>16</td>
</tr>
</tbody>
</table>

VT indicates ventricular tachycardia; LVOT, left ventricular outflow tract.
*At time of entry into the study.
†At time of death.
‡Captopril, furosemide, and warfarin.

was 0.9% per year (95% CI, 0.4% to 2.0%; P = .43). The relative risk of cardiac death for patients with VT was 1.4 compared with patients without VT (95% CI, 0.6 to 6.1) (Table 3). In the patients with VT, the sudden death rate was 1.4% per year (95% CI, 0.4% to 3.5%), and in the patients without VT it was 0.6% (95% CI, 0.2% to 1.5%) (P = .24) (Figure). The relative risk of sudden death for patients with VT compared with those without VT was 2.4 (95% CI, 0.5 to 11.9) (Table 3). This higher relative risk in patients with VT was confirmed by a stratified analysis that adjusted for age (relative risk for sudden death, 3.5; P = .13) and by a Cox multivariate model that included both age and presence of outflow obstruction at initial examination (relative risk, 2.6; P = .25).

Treatment During Follow-up
Of the 151 patients included in the study, 88 (58%) remained asymptomatic and were not treated with cardioactive medications during follow-up. Of these patients, 20 were in the group with VT and 68 in the group without VT; none of these 88 patients died.

Sixty-three patients (42%) were treated with cardioactive medications during follow-up. Nine patients with VT and 25 without VT were treated with β-blockers, and 13 patients with VT and 16 without VT were treated with verapamil. The number of patients treated with β-blockers or verapamil was not significantly different between the two groups (P = .07). Three patients on β-blockers died suddenly, 1 in the group with VT and 2 in the group without VT.

In addition, 9 patients with VT and 9 without VT who had been treated with β-blockers or verapamil also received class I or class III antiarrhythmic medications during follow-up. Amiodarone was used in 12 patients, flecainide in 4, quinidine in 1, and disopyramide in 1. Antiarrhythmic treatment was started because of non-sustained VT in 11 patients, paroxysmal atrial fibrillation in 6, and recurrent supraventricular tachycardia in 1. Of the 11 patients who were treated because of non-sustained VT, 2 did not have VT on their initial ambulatory ECG recording but showed VT during follow-up. Three patients died suddenly while they were on class I or class III antiarrhythmic medications; 1 patient was on quinidine, 1 on flecainide, and 1 on amiodarone (Table 2). Treatment with quinidine and flecainide had been started because of paroxysmal atrial fibrillation and treatment with amiodarone because of non-sustained VT.

Syncope
By selection criteria, patients with recurrent syncope or recent syncope were excluded from the study. Four (10%) of the patients with VT and 5 (5%) of those without VT who were included in the study had had a single episode of syncope > 6 months before their initial examination (P = .25). None of these 9 patients died.

Cardiac Events in the Excluded Patients
Of the 106 patients who did not meet the selection criteria, 30 were excluded because they were in functional class III or IV and 8 because they had a history of recurrent syncope or recent syncope at the time of the initial examination. In addition, 68 other patients who were in functional class I or II at initial examination were excluded because they had not had an ambulatory event for the past 6 months.

TABLE 3. Total Cardiac Mortality and Sudden Cardiac Death in Patients With VT and Patients Without VT

<table>
<thead>
<tr>
<th></th>
<th>42 Patients With VT</th>
<th></th>
<th>109 Patients Without VT</th>
<th></th>
<th>Relative Risk†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events</td>
<td>% Annual Rate</td>
<td>No. of Events</td>
<td>% Annual Rate</td>
<td>P</td>
</tr>
<tr>
<td>Total cardiac mortality (95% CI)</td>
<td>3</td>
<td>1.4 (0.4-3.5)</td>
<td>5</td>
<td>0.9 (0.4-2.0)</td>
<td>.43</td>
</tr>
<tr>
<td>Sudden cardiac death (95% CI)</td>
<td>3</td>
<td>1.4 (0.4-3.5)</td>
<td>3</td>
<td>0.6 (0.2-1.5)</td>
<td>.24</td>
</tr>
</tbody>
</table>

VT indicates ventricular tachycardia.
*For patients with VT compared with patients without VT.
VT was died of he of die.

VT.

ECC.

ECG recording (54 patients) or because they were on cardioactive medications at the time of the ambulatory ECG recording (14 patients).

Of the 106 patients excluded from the study, 3 were lost to follow-up. The remaining 103 patients were followed through December 1991 or to the time of death, as were the 151 patients included in the study. In the excluded patients, the period of follow-up ranged from 1 to 110 months (mean, 58 months). The 103 excluded patients ranged in age from 1 to 79 years (mean, 46 ± 18 years); 64 (62%) were male. Obstruction to left ventricular outflow was present in 36 patients and was absent in the remaining 67 patients.

During follow-up, 12 of the 103 excluded patients died of cardiac causes; 7 died suddenly and in congestive heart failure. Of these 12 patients, 10 had been excluded from the study because they were in functional class III or IV at initial examination, 1 because he was on cardioactive medications at the time of the ambulatory ECG recording and 1 because he had not had an ambulatory ECG recording. Of the 7 sudden cardiac deaths, 6 occurred in the patients who had been excluded from the study because they were in functional class III or IV and 1 in the patient who had been excluded because he had not had an ambulatory ECG recording.

In the excluded patients, the total cardiac mortality was 2.4% per year (95% CI, 1.4% to 3.9%). In the subgroup of 30 patients in functional class III or IV at initial examination, the total cardiac mortality (6 sudden deaths and 4 deaths due to congestive heart failure) was 5.9% per year (95% CI, 3.2% to 10.0%).

Eight other patients died of noncardiac causes; 3 died of malignancy, 2 of stroke, 1 of cerebral hemorrhage, 1 of hepatitis, and 1 in a car accident. The 2 patients who died of stroke were 76 and 79 years old, respectively, and they were both in sinus rhythm at the most recent clinical evaluation.

Discussion

The purpose of the present investigation was to assess the prognosis of those asymptomatic or only mildly symptomatic patients with hypertrophic cardiomyopathy who have nonsustained VT on ambulatory ECG monitoring. Annual mortality in our study patients with VT was low (<1.5%, with upper confidence limits <4%). About 50% of the patients with VT remained asymptomatic and were not treated with cardioactive medications during follow-up; none of these patients died. These results suggest that the presence of brief and infrequent episodes of VT is not a strong marker for increased risk of sudden death and should not be considered, per se, an indication for antiarrhythmic treatment in patients such as those included in our study.

In two previous investigations, a strong association was identified between nonsustained VT and sudden cardiac death in patients with hypertrophic cardiomyopathy. In our study, nonsustained VT was associated with a twofold to threefold increase in the risk of sudden death, even though this difference did not achieve statistical significance. This risk increase is much lower than that reported in the two previous studies, and the absolute cardiac mortality is also substantially lower. We believe that the characteristics of the patient populations included in these previous studies may explain these differences. The two previous investigations were performed at major referral centers for hypertrophic cardiomyopathy and were based on highly selected, high-risk patient populations. Our study is confined to asymptomatic or only mildly symptomatic patients and is based on a less selected population that probably reflects more closely the characteristics of the overall population of patients with hypertrophic cardiomyopathy. Therefore, the findings of the present investigation should not be viewed as conflicting with but rather as complementary to those of the two previous studies.

Almost 90% of our study patients with VT had infrequent episodes of nonsustained VT (≤5 episodes per 24 hours). This observation shows that, although nonsustained VT is common in patients with hypertrophic cardiomyopathy, the number of episodes of VT is low in most patients. Because the number of patients with frequent episodes of VT in our study population was small, we cannot draw conclusions regarding the relation between number of episodes of VT and risk of sudden death. It is reasonable to speculate, however, that the presence of a high number of episodes of nonsustained VT on ambulatory ECG monitoring might carry a less favorable prognosis than that identified in our study patients and may thus necessitate more aggressive management. In addition, it needs to be underlined that the present study does not address the potential value of nonsustained VT as a predictor of increased risk of sudden death in patients with recent or recurrent syncope and in patients with severe symptoms of heart failure.

About 10% of our overall patient population received class I or class III antiarrhythmic medications during follow-up. It is of note that 3 of the 6 study patients who died suddenly were on class I or class III antiarrhythmic medications at the time of death. In 2 patients, treatment was started because of paroxysmal atrial fibrillation and in 1, because of nonsustained VT. The small number of treated patients and events, as well as the retrospective design of the study, do not allow us to draw definitive conclusions regarding the effect of the antiarrhythmic treatment on mortality. However, the fact that 50% of the sudden deaths occurred in that small minority of our study patients who were on antiarrhythmic medications raises questions about the
efficacy as well as the potentially harmful effects of this treatment.

A collateral but important observation of the present investigation is that cardiac mortality in the overall study population was low (about 1% per year; 95% CI, 0.5% to 1.9%) during a relatively long period of follow-up. It should be underlined that this is the first report of the long-term prognosis of a large population of patients with hypertrophic cardiomyopathy who were asymptomatic or only mildly symptomatic at the time of entry into the study. Indeed, most of the literature on hypertrophic cardiomyopathy is based on highly selected patients referred to a few tertiary centers and, thus, it is focused on the worst extreme of the disease spectrum.9

The low annual mortality identified in our study population is in agreement with recent observations9,10,19 suggesting that the prognosis of many patients with hypertrophic cardiomyopathy is probably more favorable than could be inferred from most of the current literature. Since patient management and clinical decisions are based on what is known about the natural history of the disease, our findings underline the need for additional investigations aimed at clarifying the clinical course of hypertrophic cardiomyopathy in less selected study populations that reflect more closely the characteristics of the general population of patients with this disease. It is also of note that cardiac mortality was particularly high (about 6% per year) in the group of excluded patients who were in functional class III or IV at initial evaluation. This observation indirectly suggests that functional class may be more useful than other variables in assessing the risk of death in patients with hypertrophic cardiomyopathy.

The ideal study design for our investigation would have been a prospective one. The relatively rare occurrence of hypertrophic cardiomyopathy in the general population and the consequently low rate of enrollment of new patients, however, make it almost impossible to organize a prospective investigation in a sufficiently large patient population and gather the results in timely fashion. Therefore, to try to overcome this limitation, we used a study design in which the patients enrolled represent all the patients with hypertrophic cardiomyopathy who were seen at the participating institutions and met the entry criteria during a definite period of time. Therefore, we are confident that the present study population is truly representative of the patient population that would have been prospectively enrolled at our institutions.

In conclusion, our findings show that cardiac mortality is low in patients with hypertrophic cardiomyopathy who are asymptomatic or only mildly symptomatic and have brief and infrequent episodes of VT on ambulatory ECG monitoring. Our results also suggest that brief and infrequent episodes of VT should not be considered, per se, an indication to antiarrhythmic treatment in such patients.

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P Spirito, C Rapezzi, C Autore, P Bruzzi, P Bellone, P Ortolani, P V Fragola, F Chiarella, M Zoni-Berisso and A Branzi

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